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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/650,110	ZHU ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/4/03,8/18/04,9/5/06,5/24/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 17-39 are presented for examination.

Claims 7-16 have been cancelled pursuant to the amendment filed May 14, 2007.

Acknowledgement is made of Applicant's claim for benefit under 35 U.S.C. 119(e) of U.S. Provisional Patent Application No. 60/405,922, filed August 26, 2002.

Applicant's Information Disclosure Statements (IDS) filed December 4, 2003 (three pages), August 18, 2004 (nine pages), September 5, 2006 (two pages) and May 24, 2007 (two pages) have each been received and entered into the present application. As reflected by the attached, completed copies of form PTO/SB/08A-B (16 pages total), the Examiner has considered the cited references, with the exception of Cite No. 125 on the IDS filed August 18, 2004. After a reasonable search of the record, the Examiner could not locate a copy of said reference and, accordingly, it has not been further considered.

Applicant's response filed October 20, 2006 to the requirement for restriction/election dated September 22, 2006 was received and entered into the present application. An election of species of delipidated protein particle and, if applicable, additional therapeutic agent that affects lipid metabolism or parameters associated with Alzheimer's disease, was inadvertently omitted from the requirement dated September 22, 2006. Accordingly, a supplement requirement for election was set forth on January 12, 2007. Applicant's response filed May 14, 2007 to the requirement dated January 12, 2007 has been received and entered into the present application.

Requirement for Restriction/Election

Pursuant to the amendment of May 14, 2007, claims 7-16 have been cancelled and claims 17-39 are newly added. In view of the fact that the claims are now drawn to a single invention and the election of species requirement as set forth in the previous Office Action of January 12, 2007 is no longer

applicable to the instant claims, the requirement for restriction/election is hereby rendered moot and is **withdrawn**.

The claims now under examination are 17-39 and such claims will be herein examined on the merits.

Objection to the Oath/Declaration

The oath or declaration is defective because Applicant has failed to provide a post office anywhere in the application papers as required by 37 C.F.R. 1.33(a), which was in effect at the time of filing of the oath or declaration. A statement over Applicant's signature providing a complete post office address is required for each of the named inventors. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by serial number and filing date is required. Please reference MPEP §§602.01 and 602.02.

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement Requirement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of Alzheimer's disease in a patient diagnosed with Alzheimer's disease comprising administering a composition comprising partially delipidated plasma, does not reasonably provide enablement for delaying the onset of symptoms of Alzheimer's disease in a patient at risk of developing Alzheimer's disease comprising administering a composition comprising partially delipidated plasma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

The present invention is directed to a method for treating Alzheimer's disease in a patient diagnosed with the same, comprising administering to the patient an amount of a composition comprising a partially delipidated plasma having a lower content of at least one of triglycerides or cholesterol than a naturally occurring plasma, wherein the amount is effective to treat the Alzheimer's disease in the patient. The present invention is further directed to a method for delaying the onset of symptoms of Alzheimer's disease in a patient at risk of developing Alzheimer's disease comprising administering a composition comprising a partially delipidated plasma having a lower content of at least one of triglycerides or cholesterol than a naturally occurring plasma, wherein the amount is effective to delay the onset of symptoms of the Alzheimer's disease in the patient.

In particular, one skilled in the art could not practice the presently claimed subject matter of delaying the development or onset of Alzheimer's disease by administering the claimed delipidated plasma composition without undue experimentation because the artisan would not accept on its face that delaying the development or onset of Alzheimer's disease could actually be achieved given the state of

the art at the time of the invention. Based upon the state of the art, as discussed below, and the evidence presented by Applicant, the artisan would have only accepted that the condition could be treated with such a delipidated plasma composition.

As set forth in *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains the teachings of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112, *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support;* assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added)

The present claims circumscribe the use and administration of the presently claimed delipidated plasma composition for delaying the development and/or onset of Alzheimer's disease. That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that by administering a pharmaceutical composition comprising the presently claimed delipidated plasma that amyloid plaques characteristic of Alzheimer's disease would actually be prevented from developing or worsening or that the onset of Alzheimer's disease could be prevented. In other words, the skilled artisan would have understood the phrase "delaying the onset of", in their broadest reasonable interpretation consistent with MPEP §2111, to mean that the incidence or progression of amyloid plaques and/or Alzheimer's disease after administration of the presently claimed delipidated plasma composition would essentially be 0% and could be reasonably expected not to develop, occur or recur. In light of the fact that the specification fails to provide the skilled artisan with any direction or guidance as to how the delay of formation and/or onset of amyloid plaques or Alzheimer's disease could actually be achieved, since the

disclosure is solely directed to the concept of treatment in patients that already exhibit such plaques and are diagnosed with Alzheimer's disease, the present specification is viewed as lacking an enabling disclosure of the entire scope of the claimed invention.

Regarding delaying the formation of amyloid plaques or the onset of Alzheimer's disease, the objective truth that the development of such plaques or of Alzheimer's disease could be prevented from occurring or that amyloid fibrils could be eliminated is doubted because, while the state of the art with regard to the reduction of amyloid deposits associated with Alzheimer's disease may be achieved and, thus, treat the condition in patients diagnosed with such a disease, the state of the art with regard to the definitive delaying of the formation of such deposits (in essence, the prevention of developing or worsening of Alzheimer's disease) or delaying the onset of Alzheimer's disease is grossly underdeveloped.

The objective truth of the statement that Alzheimer's disease may be prevented or can be delayed from developing is doubted because the disease is particularly elusive and manifests itself in a variety of different ways in different subjects such that the diagnostician cannot be sure that the disease is truly the cause of the signs and symptoms of disorder exhibited by the patient. A diagnosis of Alzheimer's disease is tentative, at best, until confirmation of the diagnosis can be confirmed by the presence of amyloid deposits in the brain at autopsy (see Cecil's Textbook of Medicine, "Differential Diagnosis", page 2043 at column 1).

Such difficulties in diagnosis are recognized in the art. Applicant's attention is drawn to Cecil's Textbook of Medicine, which states, "In a patient with clinical findings suggesting Alzheimer's disease, other causes of dementia should be excluded by history, examination, and the laboratory studies described above. CSF evaluation for amyloid protein and tau protein can increase the likelihood of a diagnosis of Alzheimer's disease, but they are not sufficiently specific to be of routine value in screening or early diagnosis of Alzheimer's disease...Presence of the apoE4 allele makes it very likely that the patient's

dementia is produced by Alzheimer's disease. ApoE testing does not have predictive value for asymptomatic individuals." (see Cecil's Textbook of Medicine, "Diagnosis", column 2 at page 2044)

In this regard, it is also noted that the art acknowledges only certain criteria for definitive diagnosis of Alzheimer's disease, see in particular Gauthier et al., (Can. Med. Assoc. J, Oct 15, 1997, 157(8): 1047-52), Greicius et al. (J Neurol. Neurosurg. Psychiatry, 2002 Jun; 72(6):691-700) and Gasparini et al. (FASEB J., 12, Jan. 1998, pp. 17-34). Post mortem analysis of brain tissue for the characteristics of amyloid plaques is considered necessary for a definitive diagnosis. This is because the art has come to recognize its presence in essentially all cases. However, to achieve diagnostic status took years of evaluative procedures, both pre- and post-mortem, confirming that every case had a degree of this pathology. Even so, diagnostic application is often problematic given variable peptide expression patterns among clinically similar and dissimilar diseases states (see Greicius et al.).

Given that there a only a few factors that are recognized to have moderate, if any, predictive value in determining the likelihood that patients develop such a disease or to even determine whether patients actually have such a disease, since many of the early signs of Alzheimer's disease are common complaints of aging or result from other neurological conditions, such as depression, where memory impairment is not present (see Cecil's Textbook of Medicine, "Evaluation of Dementia", column 1, page 2042), one of ordinary skill in the art would not accept on its face Applicant's statement that the onset of Alzheimer's disease could be delayed and/or prevented using the presently claimed composition of delipidated plasma. In fact, such complexity of diagnosis precludes a common, art-accepted protocol for preventing or delaying the onset of Alzheimer's disease in any patient, given that the circumstances or risk factors are unique to that individual and must be considered on a case-by-case basis when determining the most effective approach to delaying or preventing Alzheimer's disease.

In other words, not only is the population in need of such treatment not particularly well defined in the art because of the difficulties associated with making an accurate diagnosis, but the disease is also

sufficiently complicated and poorly understood such that the idea that any active agent (including that presently claimed) would be capable of delaying or preventing the onset of such a condition via administration of the presently claimed composition would not have been reasonably expected by the skilled artisan. The artisan would have required sufficient direction as to how the administration of the presently claimed active composition of delipidated plasma could actually determine the population of patients in need of such delay or prevention and how the presently claimed composition could actually delay or prevent Alzheimer's disease such that the artisan would have been imbued with at least a reasonable expectation of success. Such success would not have been reasonably expected given that the concept of a single agent, or even a combination of agents, that is effective against the development of Alzheimer's disease would have been unique and, thus, met with a great deal of skepticism.

It is in this regard that Applicant is directed to the MPEP at §2164.08. All questions of enablement are evaluated against the claimed subject matter. Concerning the breadth of a claim relevant to enablement, the only relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of enablement involved the determination of how broad the claim is with respect to the disclosure and the determination of whether one skilled in the art is enabled to use the *entire scope* of the claimed invention without undue experimentation.

Applicant provides various studies in the specification directed to the use of the claimed delipidated plasma composition for reducing serum cholesterol, treating atherosclerosis and additional studies of the delipidated plasma product prophetically predicted to reduce plasma lipids, plasma cholesterol, ApoE and amyloid-beta protein. Results of these studies demonstrated that the claimed delipidated plasma composition was capable, or was at least predicted to be capable of, reducing serum lipids and amyloid-beta concentrations such that a concomitant reduction in Alzheimer's disease

pathology would have been reasonably expected and/or correlated to such activity. Please see pages 24-33 of the specification.

However, none of these studies demonstrates the ability of the claimed delipidated plasma composition to effectively delay the onset of Alzheimer's disease. While a lack of a working embodiment cannot be the sole factor in determining enablement, the absence of substantial evidence commensurate in scope with the presently claimed subject matter, in light of the unpredictable nature of the art and the direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole. The instant specification conspicuously lacks any disclosure or teaching of manner and process of using the presently claimed compounds for achieving the objective of delaying the onset of Alzheimer's disease itself. Nowhere does the specification disclose the manner or procedure of using the presently claimed delipidated plasma composition for delaying the onset of Alzheimer's such that the skilled artisan would have been imbued with at least a reasonable expectation of success in determining those patients population in need of delayed onset of Alzheimer's disease without the burden of an undue level of experimentation.

The basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the pharmaceutical and chemical arts that experimentation in this particular art is not at all uncommon, but that the level of experimentation required in order to practice this aspect of the invention in the absence of any enabling direction by Applicant would be *undue*. Please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (emphasis added)

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor with several years of experience in the art.

As the cited art and discussion of the above factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that the objectives of delaying the onset of Alzheimer's disease in a subject using the claimed delipidated plasma composition could be achieved. In order to actually achieve such a result, it is clear from the discussion above that the skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse but the impermissible burden of undue experimentation in order to practice the full scope of the presently claimed invention.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-22, 25-33 and 36-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention.

Present claim 17 is directed to a method for treating Alzheimer's disease, comprising administering a composition comprising a partially delipidated plasma having a lower content of at least one of triglycerides or cholesterol than a naturally occurring plasma. Present claim 28 is directed to a method for delaying the onset of Alzheimer's disease comprising administration of the same.

In particular, the phrase "naturally occurring plasma" renders the claim indefinite because the source of the "naturally occurring plasma" is not clearly delineated by the claim. Since plasma does not occur in nature outside of the body of a living mammal with a functioning circulatory system, it is unclear how such plasma could not be derived from a particular source of plasma and, thus, be "naturally occurring". Accordingly, the claims fail to clearly define what is intended to be encompassed by the term "naturally occurring plasma" such that one of ordinary skill in the art at the time of the invention would

have been immediately apprised of the metes and bounds of the claimed subject matter and, further, such that the skilled artisan would have been able to use the "naturally occurring plasma" as a standard by which to measure the lipid content of the delipidated plasma composition.

It is further noted that present claims 23-24 and 34-35 are not subject to this rejection because said claims specifically recite that the "naturally occurring plasma" is yielded from the separation of blood cells from the whole blood obtained from a patient.

For these reasons, claims 17-22, 25-33 and 36-39 fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claims 26 and 37 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention.

Present claims 26 and 37 are directed to the practice of the claimed methods in a subject with increased blood cholesterol.

The term "increased" in claims 26 and 37 is a relative term that renders the claim indefinite because the claims fail to define any standard for ascertaining the requisite amount of cholesterol tolerated by the claims and still be considered "increased" cholesterol levels. Further, the specification fails to provide any disclosure of such a standard by which to determine if a patient's cholesterol level is considered "increased" or not. Accordingly, one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

For these reasons, claims 26 and 37 fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

For the purposes of examination, claims 26 and 37 will be interpreted as reading upon the treatment of a patient with higher-than-normal cholesterol levels.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17-27 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cham (U.S. Patent No. 4,895,558; 1990) in view of Simons et al. ("Cholesterol and Alzheimer's Disease: Is There a Link?", *Neurology*, 57; 2001:1089-1093).

Cham teaches a method for autologous plasma delipidation of animals, including humans (abstract), comprising drawing blood from the animal, separating the plasma from the red blood cells, delipidating the plasma with a lipid solvent, remixing the delipidated plasma with the red blood cells and re-introducing the delipidated blood back into the animal (abstract, col.3, l.27-36), such as, e.g., via intravenous infusion (col.4, l.38-41), wherein the delipidation step comprises mixing the plasma with the liquid solvent, allowing the mixture to separate into an organic solvent/lipid phase and an aqueous delipidated plasma phase and drawing off the organic phase (col.3, l.37-42), such as, e.g., via distillation (col.8, l.36-39). Cham further teaches that the use of a biphasic solvent system for extraction attains complete removal of cholesterol, triglyceride, phospholipid and non-esterified fatty acids in the absence

of protein denaturation (col.2, l.50-55). Cham discloses the use of butanol-DIPE (di-isopropylether) as the preferred solvent in a 40%:60% (V/V) ratio (col.4, l.8-12) and further discloses that the use of the butanol-DIPE solvent system results in partial delipidation of LDL and HDL (col.6, l.3-25). Exemplary uses of the disclosed plasma delipidation process include, e.g., reversing atherosclerosis (col.3, l.16-20, col.6, l.26-36) and/or reducing the likelihood of heart attacks or strokes (col.8, l.51-60).

Simons et al. teaches that amyloid-beta is the main component of amyloid plaques (abstract), which are characteristic of Alzheimer's disease (col.1, p.1089, para.1), and contributes to neurodegeneration (col.1, p.1089, para.1) and senile plaque formation (col.2, p.1089, para.1). Simons et al. further discloses two studies that demonstrated a decreased prevalence of Alzheimer's disease associated with the use of cholesterol-lowering drugs, such as, e.g., statins (abstract, col.1, p.1091, para.4). Simons et al. teaches that decreased neuronal cholesterol levels inhibits the amyloid-beta forming amyloidogenic pathway by removing amyloid precursor protein (APP) from cholesterol- and sphingolipid-enriched membrane microdomains and that such depletion of cellular cholesterol levels reduces the ability of amyloid-beta to act as a seed for further fibril formation (abstract).

One of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ the autologous plasma delipidation process of Cham in a patient suffering from Alzheimer's disease as a means for reducing serum and cellular cholesterol levels to thereby treat the disease. Such a person would have been motivated to do so because the prior art of Simons et al. clearly recognizes the contribution that elevated cholesterol has in effecting an increase in the production and formation of amyloid-beta deposits. Further, the skilled artisan would have had a reasonable expectation of success in treating the condition because the reduction of amyloid-beta deposits, which are known to lead to the deleterious neurodegenerative effects of Alzheimer's disease, such as, e.g., senility (i.e., dementia), as evidenced by Simons et al., would have ameliorated, or at least slowed the progression of, the neurodegeneration associated with the condition.

Further, the treatment of a person suffering from Alzheimer's disease and exhibiting higher-than-normal cholesterol levels (claim 26) with the plasma delipidation procedure disclosed by Cham would have naturally commended itself to one of ordinary skill in the art at the time of the invention because such a person would have readily recognized that such an excess of circulating cholesterol would have accelerated the course of the disease by increasing the formation of amyloid-beta deposits in the brain. Thus, the skilled artisan would have been motivated to reduce such elevated cholesterol levels so as to inhibit the formation of said deposits and the progression of the disease.

Double Patenting

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Non-Provisional Rejections

Claims 17-27 and 39 are provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 4,895,558; claims 1-12 of U.S. Patent No. 5,744,038; claims 1-48 of U.S. RE37,584; or claims 1-8, 19-33 and 41-47 of US RE39,498, each alternatively in view of Simons et al. ("Cholesterol and Alzheimer's Disease: Is There a Link?", *Neurology*, 57; 2001:1089-1093).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims

because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the cited patents are not considered patentably distinct from each other because the pending claims are rendered obvious by the patented claims.

The claims of each of the cited patents clearly provide for methods of delipidating animal plasma, i.e., removal of cholesterol, triglycerides, and/or other lipids, via the withdrawal of blood from the subject, separating out the blood cells and mixing the plasma with a solvent, such as, e.g., an ether or an ether and alcohol mixture, and then returning the delipidated plasma fraction back into the animal.

Though the patented claims do not disclose the use of the delipidated plasma fraction for the treatment of a patient suffering from Alzheimer's disease, Simons et al. is relied upon for its teachings that decreased neuronal cholesterol levels inhibits the amyloid-beta forming amyloidogenic pathway by removing amyloid precursor protein (APP) from cholesterol- and sphingolipid-enriched membrane microdomains and that such depletion of cellular cholesterol levels reduces the ability of amyloid-beta to act as a seed for further fibril formation (abstract) and that amyloid-beta is the main component of amyloid plaques (abstract), which are characteristic of Alzheimer's disease (col.1, p.1089, para.1), and contribute to neurodegeneration (col.1, p.1089, para.1) and senile plaque formation (col.2, p.1089, para.1).

Accordingly, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to employ the plasma delipidation process(es) of the patented claims in a patient suffering from Alzheimer's disease as a means for reducing serum and cellular cholesterol levels to thereby treat the disease. Such a person would have been motivated to do so because the prior art of Simons et al. clearly acknowledges the contribution that elevated cholesterol has in effecting an increase in the production and formation of amyloid-beta deposits. Further, the skilled artisan would have had a

reasonable expectation of success in treating the condition because the reduction of amyloid-beta deposits, which are known to lead to the deleterious neurodegenerative effects of Alzheimer's disease, such as, e.g., senility (i.e., dementia), would have ameliorated, or at least slowed the progression of, the neurodegeneration associated with the condition.

Additionally, the treatment of a person suffering from Alzheimer's disease and exhibiting increased cholesterol levels (claim 26) with the plasma delipidation procedure(s) of the patented claims would have naturally commended itself to one of ordinary skill in the art because such a person would have readily recognized that such an excess of circulating cholesterol would have accelerated the course of the disease by increasing the formation of amyloid-beta deposits in the brain. Thus, the skilled artisan would have been motivated to reduce such elevated cholesterol levels so as to inhibit the formation of said deposits and the progression of the disease.

Accordingly, rejection of claims 17-27 and 39 is proper over claims 1-3 of U.S. Patent No. 4,895,558; claims 1-12 of U.S. Patent No. 5,744,038; claims 1-48 of U.S. RE37,584; or claims 1-8, 19-33 and 41-47 of US RE39,498 as claiming obvious and unpatentable variants thereof.

Conclusion

The prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Please reference U.S. Patent Application Publication No. 2003/0127390 to Davis JR. ("Rheological Treatment Methods and Related Apheresis Systems").

Rejection of claims 17-39 is proper.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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